



## UNITED STATES DEPARTMENT OF COMMERCE

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APPLICATION NUMBER	FILING DATE	FIRST NAMED APPLICANT	ATTY. DOCKET NO.
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09/223,957 12/31/98 DALE

R OLIG-0004

EXAMINER

HM12/0817

BOZICEVIC & REED  
285 HAMILTON AVENUE  
SUITE 200  
PALO ALTO CA 94301

ART UNIT PAPER NUMBER

1623

DATE MAILED:

08/17/99

This is a communication from the examiner in charge of your application.  
COMMISSIONER OF PATENTS AND TRADEMARKS

## OFFICE ACTION SUMMARY

- ☒ Responsive to communication(s) filed on 6-21-99 and 6-17-99
- ☒ This action is **FINAL**

- ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 D.C. 11; 453 O.G. 213.

A shortened statutory period for response to this action is set to expire THREE month(s), or thirty days, whichever is longer, from the mailing date of this communication. Failure to respond within the period for response will cause the application to become abandoned. (35 U.S.C. § 133). Extensions of time may be obtained under the provisions of 37 CFR 1.136(a).

## Disposition of Claims

- ☒ Claim(s) 1-4 and 6-21 is/are pending in the application.
- Of the above, claim(s) \_\_\_\_\_ is/are withdrawn from consideration.
- ☐ Claim(s) \_\_\_\_\_ is/are allowed.
- ☒ Claim(s) 1-4 and 6-21 is/are rejected.
- ☐ Claim(s) \_\_\_\_\_ is/are objected to.
- ☐ Claim(s) \_\_\_\_\_ are subject to restriction or election requirement.

## Application Papers

- ☐ See the attached Notice of Draftsperson's Patent Drawing Review, PTO-948.
- ☐ The drawing(s) filed on \_\_\_\_\_ is/are objected to by the Examiner.
- ☐ The proposed drawing correction, filed on \_\_\_\_\_ is ☐ approved ☐ disapproved.
- ☐ The specification is objected to by the Examiner.
- ☐ The oath or declaration is objected to by the Examiner.

## Priority under 35 U.S.C. § 119

- ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d).
- ☐ All ☐ Some\* ☐ None of the CERTIFIED copies of the priority documents have been
- ☐ received.
- ☐ received in Application No. (Series Code/Serial Number) \_\_\_\_\_
- ☐ received in this national stage application from the International Bureau (PCT Rule 17.2(a)).

\*Certified copies not received: \_\_\_\_\_

- ☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e).

## Attachment(s)

- ☒ Notice of Reference Cited, PTO-892
- ☒ Information Disclosure Statement(s), PTO-1449, Paper No(s). 3
- ☐ Interview Summary, PTO-413
- ☐ Notice of Draftsperson's Patent Drawing Review, PTO-948
- ☐ Notice of Informal Patent Application, PTO-152

-SEE OFFICE ACTION ON THE FOLLOWING PAGES--

09/223,957  
PTOL-328 (Rev. 9/98)

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Applicant's amendment A filed 6-16-99 and the IDS filed 4-30-99 have been received and entered into the record.

All 35 USC statutes not cited in this Office action can be found cited in full in a previous Office action.

Claims 1 - 4 and 6 - 21 are pending in the case.

***35 USC 103 Rejection***

Claims 1 - 4 and 6 - 20 stand rejected under 35 USC 103 over applicant's own prior art admissions on the record at page 2, first paragraph; page 12, lines 1 - 14; and page 14, last paragraph for the reasons already of record on pages 2 - 4 of the Office action mailed 3-17-99.

The applicant first argues that they are not just claiming a desalting process, but are claiming a combination of purifying nucleic acids from a strong anion exchange resin followed by the desalting of said oligos on a hydrophobic material. It appears that applicant believes that taking an eluate containing a nucleic acid in a high salt solution from a strong anion exchange column and then going directly onto a strongly hydrophobic matrix in order to both concentrate and desalt is the point of novelty and non-obviousness. This argument has been fully considered but is not deemed persuasive. First of all, it does not matter how the nucleic acid acquired a high salt solution, i.e., from high salt elution from an anion exchange column or from dialysis, the point is that the prior art clearly teaches the desalting of nucleic acids using a strongly hydrophobic matrix. As further substantiation of this fact, the examiner cites two prior art patents (Hatzenbuhler et al. 5,275,946 at column 6, lines 4 - 10; Padmapriya et al. 5,929,226, column 12,

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lines 12 - 13). Each of these patents briefly mentions the use of Waters' SepPak C<sub>18</sub> for desalting oligonucleotides as if the technique is ordinary and routine. Neither of these patents provides the details for this desalting technique routine prior to applicant's filing date. However, The Lineberger Nucleic Acids Core Facility web site (<http://metalab.unc.edu/nacf/>) does provide the full details of this desalting procedure on a strongly hydrophobic matrix (see attachment). The oligo is placed into a very high salt solution, added to the Sep-Pak, washed with distilled water, and then eluted with 60% aqueous methanol. The person of ordinary skill in the art would understand that if an oligo eluate from strong anion exchange column already content a high content of salt, no additional salt would need to be added prior to binding the oligo to the hydrophobic matrix.

The applicant further argues that the instantly claimed method obviates the use of volatile organic buffers, significantly reducing the time necessary to complete the procedure as compared to existing methods of reverse phase capture. This argument has been fully considered but is not deemed persuasive. As discussed above, the Waters Sep-Pak technique does not use volatile organic buffers, such as ammonium carbonate, but instead, uses aqueous organic solvents, i.e., aqueous methanol.

The applicant further argues that there has been a longstanding need in the art of oligonucleotide synthesis for a simple, rapid, desalting/concentration method as discussed at the IBC 2nd Annual Conference on Oligonucleotide Technologies. This argument has been fully considered but is not deemed persuasive. The comparative table used in this

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presentation indicates that one of the limitations of reverse phase capture is the necessity for the removal of organics. Unfortunately, there is no definition of “organics” in this context. But regardless, the two cited prior art patents combined with the protocol for use of the Sep-Pak for desalting oligos argues that there was just such a method available at the time of the invention. Furthermore, applicant’s preferred embodiment uses an aqueous ethanol solution for eluting from the hydrophobic material. Claim 18 recites n-propanol, isopropanol, a methanol. Claim 19 recites only ethanol. The substitution of other lower alcohols for the methanol of the Waters Sep-Pak protocol would certainly not be an inventive step, but merely a choice of equivalent options based primarily on cost and/or environmental safety. However, propanol and methanol are both toxic compounds to humans, in contrast to applicant’s use of the term “non-toxic” in claim 18. Only the use of water alone as the eluent (claim 6) appears to offer any substantive difference of applicant’s method over that of the prior art. However, even this too would have been obvious to the person of ordinary skill in the art wanting to reduce costs (water is always cheaper than any other solvent) in the desalting/concentration of oligos by simply selecting a hydrophobic material less hydrophobic than Waters C18 material that would permit elution with water alone. The disadvantage of water alone is that it takes longer to remove the water by freeze drying or by evaporation under reduced pressure.

In summary, It would have been obvious to the person of ordinary skill in the art at the time of the invention to have modified the prior art procedure of Waters by adjusting either the eluting solution or the degree of hydrophobicity of the matrix in order to achieve the rapid

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desalting and concentration of oligonucleotides, eluting with either an aqueous alcohol or even water itself, depending upon influence of two competing motivations--to minimize cost and environmental damage versus minimizing the removal of the eluent. Thus, the instant claims are prima facie obvious in the absence of clear and convincing evidence to the contrary. The proffered long-felt need in the art is contradicted by the clear prior art methods of desalting on a Waters Sep-Pak.

**THIS ACTION IS MADE FINAL.** Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire **THREE MONTHS** from the mailing date of this action. In the event a first reply is filed within **TWO MONTHS** of the mailing date of this final action and the advisory action is not mailed until after the end of the **THREE-MONTH** shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than **SIX MONTHS** from the mailing date of this final action.

No claim is allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Examiner Kunz, whose telephone number is (703) 308-4623. The examiner

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can normally be reached on Tuesday through Friday from 6:30 AM to 4:00 PM. The examiner can also be reached on alternate Mondays.

If attempts to reach the examiner by telephone are unsuccessful, a supervisory examiner can be reached: Cecilia Tsang at (703) 308-0254 or Gary Jones at (703) 308-1152. The fax phone number for this Group is (703) 308-4556.

Any inquiry of a general nature or relating to the status of this application should be directed to the Group receptionist whose telephone number is (703) 308-1235.

*Gary L. Kunz*  
GARY L. KUNZ  
PRIMARY EXAMINER  
GROUP 1200